

In the specification:

Please replace the paragraph spanning lines 10-20 of page 4, with the following amended paragraph:

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The present invention provides isolated nucleic acid molecules comprising or alternatively consisting of, polynucleotides encoding TR11, TR11SV1, and TR11SV2 receptors having the amino acid sequences shown in Figures 1A and 1B (SEQ ID NO:2), 2A and 2B (SEQ ID NO:4), and 3A and 3B (SEQ ID NO:6), respectively, or the amino acid sequences encoded by the cDNA clones encoding the TR11, TR11SV1, and TR11SV2 receptors, respectively, deposited as ATCC Deposit Numbers 209341, 209343 and 209342, respectively, on October 7, 1997. The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them for production of TR11, TR11SV1, and TR11SV2 polypeptides or peptides by recombinant techniques.

Please replace the paragraph spanning lines 7-25 of page 10, with the following amended paragraph:

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The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding TR11, TR11SV1, and TR11SV2 polypeptides (Figures 1A and 1B, 2A and 2B, and 3A and 3B (SEQ ID NO:2, SEQ ID NO:4, and SEQ ID NO:6, respectively)), the amino acid sequences of which were determined by sequencing cloned cDNAs. The TR11, TR11SV1, and TR11SV2 proteins shown in Figures 1A and 1B, 2A and 2B, and 3A and 3B, respectively, share sequence homology with the human mGIR receptor-like protein (Figure 2 (SEQ ID NO:7)). On October 7, 1997, deposits of plasmid DNAs encoding TR11, TR11SV1, and TR11SV2 were made at the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, and given accession numbers 209341, 209343 and 209342, respectively. The nucleotide sequences shown in Figures 1A and 1B, 2A and 2B, and 3A and 3B (SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5, respectively) were obtained by sequencing cDNA clones (Clone ID HHEAC71, HCFAZ22 and HT5EA78, respectively) containing the same amino acid coding sequences as the clones in ATCC Accession Nos. 209341,

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209343 and 209342, respectively. The deposited clone encoding TR11 is contained in the pCMVSPORT3.0 plasmid (Life Technologies, Rockville, MD). The deposited clone encoding TR11SV1 is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The deposited clone encoding TR11SV2 is contained in the pSport1 plasmid (Life Technologies, Rockville, MD).

Please replace the paragraph bridging pages 12-13, with the following amended paragraph:

As indicated, the present invention also provides mature forms of the TR11 and TR11SV2 receptors of the present invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species on the protein. Further, it has long been known that the cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide. Therefore, the present invention provides nucleotide sequences encoding mature TR11 and TR11SV2 polypeptides having the amino acid sequences encoded by the cDNA clones contained in ATCC Deposit Numbers 209341 and 209342 and as shown in Figures 1A and 1B and 3A and 3B, respectively (SEQ ID NO:2 and SEQ ID NO:6, respectively). By the mature TR11 and TR11SV2 polypeptides having the amino acid sequences encoded by "the cDNA clones contained in ATCC Deposit Numbers 209341 and 209342" is meant the mature form(s) of the TR11 and TR11SV2 receptors produced by expression in a mammalian cell (e.g., COS cells, as described below) of the complete open reading frame encoded by the human DNA sequence of the deposited clones.

Please replace the paragraph spanning lines 6-16 of page 14, with the following amended paragraph:

As one of ordinary skill would appreciate, however, due to the possibilities of sequencing errors, as well as the variability of cleavage sites for leaders in different known proteins, the TR11, TR11SV1, and TR11SV2 receptor polypeptides encoded by the cDNAs of ATCC Deposit Numbers 209341, 209343 and 209342, respectively, comprise about 241 amino acids (but may be anywhere in the range of 224 to 251 amino acids), about 241 amino acids (but may be anywhere in the range of 231 to 251 amino acids), and about 240 amino acids (but may be anywhere in the range of 230 to 250 amino acids). Further, the predicted leader sequences of these proteins are about 25, 0, and 19 amino acids, but the actual leaders may be anywhere in the range of about 15 to about 35, about 20 to about 40, and about 9 to about 29 amino acids, respectively.

Please replace the paragraph bridging pages 15-16, with the following amended paragraph:

In another aspect, the invention provides isolated nucleic acid molecules encoding the TR11, TR11SV1, and TR11SV2 polypeptides having the amino acid sequence encoded by the cDNA clones contained in the plasmids deposited as ATCC Deposit Nos. 209341, 209343 and 209342, respectively, on October 7, 1997. In a further embodiment, these nucleic acid molecules will encode a mature polypeptide or the full-length polypeptide lacking the N-terminal methionine. The invention further provides isolated nucleic acid molecules having the nucleotide sequences shown in Figures 1A and 1B (SEQ ID NO:1), 2A and 2B (SEQ ID NO:3), and 3A and 3B (SEQ ID NO:5), the nucleotide sequences of the cDNAs contained in the above-described deposited clones; or nucleic acid molecules having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful as probes for gene mapping, by *in situ* hybridization with chromosomes, and for detecting expression of the TR11, TR11SV1, and TR11SV2 receptor genes of the present invention in human tissue, for instance, by Northern blot analysis.

Please replace the paragraph bridging pages 21-22 with the following amended paragraph:

Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 80%, 85% or 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical to: (a) a nucleotide sequence encoding the TR11 polypeptide having the complete amino acid sequence shown in Figures 1A and 1B (amino acid residues -25 to 209 in SEQ ID NO:2); (b) a nucleotide sequence encoding the TR11SV1 polypeptide having the complete amino acid sequence shown in Figures 2A and 2B (amino acid residues 1 to 241 in SEQ ID NO:4); (c) a nucleotide sequence encoding the TR11SV2 polypeptide having the complete amino acid sequence shown in Figures 3A and 3B (amino acid residues -19 to 221 in SEQ ID NO:6); (d) a nucleotide encoding the complete amino sequence shown in Figures 1A and 1B but lacking the N-terminal methionine (i.e., amino acids -24 to 209 in SEQ ID NO:2); (e) a nucleotide encoding the complete amino sequence shown in Figures 2A and 2B but lacking the N-terminal methionine (i.e., amino acids 2 to 241 in SEQ ID NO:4); (f) a nucleotide encoding the complete amino sequence shown in Figures 3A and 3B but lacking the N-terminal methionine (i.e., amino acids -18 to 221 in SEQ ID NO:6); (g) a nucleotide sequence encoding the predicted mature TR11 receptor comprising the amino acid sequence at positions from 26 to 234 in Figures 1A and 1B (amino acid residues 1 to 209 in SEQ ID NO:2); (h) a nucleotide sequence encoding the predicted mature TR11SV1 receptor comprising the amino acid sequence at positions from 1 to 241 in Figures 2A and 2B (amino acid residues 1 to 241 in SEQ ID NO:4); (i) a nucleotide sequence encoding the predicted mature TR11SV2 receptor comprising the amino acid sequence at positions from 20 to 240 in Figures 3A and 3B (amino acid residues 1 to 221 in SEQ ID NO:6); (j) a nucleotide sequence encoding the TR11 polypeptide having the complete amino acid sequence including the leader encoded by the cDNA clone contained in ATCC Deposit Number 209341; (k) a nucleotide sequence encoding the TR11SV1 polypeptide having the complete amino acid sequence including the leader encoded by the cDNA clone contained in ATCC Deposit Number 209343; (l) a nucleotide sequence encoding the TR11SV2 polypeptide having the complete amino acid sequence including the leader encoded by the cDNA clone contained in ATCC Deposit Number 209342; (m) a nucleotide sequence encoding the mature TR11 receptor having the amino acid sequences encoded by the cDNA clone contained in ATCC Deposit Number 209341; (n) a nucleotide sequence encoding the mature TR11SV1 receptor having the amino acid sequences encoded by the cDNA clone contained in

ATCC Deposit Number 209343; (o) a nucleotide sequence encoding the mature TR11SV2 receptor having the amino acid sequences encoded by the cDNA clone contained in ATCC Deposit Number 209342; (p) a nucleotide sequence encoding the TR11 receptor extracellular domain; (q) a nucleotide sequence encoding the TR11SV1 receptor extracellular domain; (r) a nucleotide sequence encoding the TR11SV2 receptor extracellular domain; (s) a nucleotide sequence encoding the TR11 receptor transmembrane domain; (t) a nucleotide sequence encoding the TR11SV1 receptor transmembrane domain; (u) a nucleotide sequence encoding the TR11SV2 receptor transmembrane domain; (v) a nucleotide sequence encoding the TR11 receptor intracellular domain; (w) a nucleotide sequence encoding the TR11SV1 receptor intracellular domain; (x) a nucleotide sequence encoding the TR11SV2 receptor intracellular domain; (y) a nucleotide sequence encoding the TR11 receptor extracellular and intracellular domains with all or part of the transmembrane domain deleted; (z) a nucleotide sequence encoding the TR11SV1 receptor extracellular and intracellular domains with all or part of the transmembrane domain deleted; (aa) a nucleotide sequence encoding the TR11SV2 receptor extracellular and intracellular domains with all or part of the transmembrane domain deleted; and (bb) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u), (v), (w), (x), (y), (z) or (aa). Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Please replace the paragraph spanning lines 1-36 of page 40, with the following amended paragraph:

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations

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with and/or between the TR11, TR11SV1 and/or TR11SV2 polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the TR11, TR11SV1 and/or TR11SV2 polypeptide sequences (e.g., those recited in SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, or contained in the respective TR11, TR11SV1 and TR11SV2 polypeptides encoded by the respective clones HHEAC71, HCFAZ22 and HT5EA78). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a TR11, TR11SV1 or TR11SV2 fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a TR11-Fc, TR11SV1-Fc or TR11SV2-Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more TR11, TR11SV1, TR11SV2 polypeptides of the invention are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include, but are not limited to, those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple TR11, TR11SV1, TR11SV2 polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

Please replace the paragraph spanning lines 3-18 of page 76, with the following amended paragraph:

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Preferably, the polynucleotides of the invention (including TR11, TR11SV1 and/or TR11SV2 fragments, variants, derivatives and analogs) encode a polypeptide which demonstrates a TR11, TR11SV1 and/or TR11SV2 functional activity. By a

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polypeptide demonstrating "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length and/or secreted TR11, TR11SV1 and/or TR11SV2 polypeptide. Such functional activities include, but are not limited to, biological activity (e.g., ability to regulate (i.e., stimulate or inhibit) B cell proliferation (e.g., see Example 31), differentiation, activation, and/or survival), antigenicity [ability to bind (or compete with a TR11, TR11SV1 and/or TR11SV2 polypeptide for binding) to an anti-TR11 antibody, anti-TR11SV1 antibody and/or anti-TR11SV2 antibody], immunogenicity (ability to generate antibody which binds to a TR11, TR11SV1 and/or TR11SV2 polypeptide), ability to form multimers with TR11, TR11SV1 and/or TR11SV2 polypeptides of the invention, and ability to bind to a receptor or ligand for a TR11, TR11SV1 and/or TR11SV2 (e.g., Endokine-alpha (See, International Publication No. WO 98/07880 and Example 27)).

Please replace the paragraph spanning lines 1-9 of page 77, with the following amended paragraph:

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In another embodiment, where a TR11, TR11SV1 and/or TR11SV2 ligand is identified (e.g., Endokine-alpha (See, International Publication No. WO 98/07880 and Example 27)), or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., 1995, Microbiol. Rev. 59:94-123. In another embodiment, physiological correlates of TR11, TR11SV1 and/or TR11SV2 binding to its substrates (signal transduction) can be assayed.

Please replace the paragraph spanning lines 25-37 of page 83, with the following amended paragraph:

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The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:4, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 209343 or encoded by a polynucleotide that hybridizes to

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the complement of the sequence of SEQ ID NO:3 or contained in ATCC deposit No. 209343 under stringent hybridization conditions or lower stringency hybridization conditions as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:3), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined *supra*.

Please replace the paragraph spanning lines 1-13 of page 84, with the following amended paragraph:

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The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:6, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 209342 or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:5 or contained in ATCC deposit No. 209342 under stringent hybridization conditions or lower stringency hybridization conditions as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:5), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined *supra*.

Please replace the paragraph spanning lines 17-32 of page 136, with the following amended paragraph:

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In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in TR11, TR11SV1 and/or TR11SV2, or the complementary strand thereof, and/or to nucleotide sequences contained